Uitgangsvraag 3: Welke prognostische factoren moeten er beschreven worden in het pa-verslag van het resectiepreparaat van HCC patiënten?

Primaire studies

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Minagawa 2007	• Retrospective single cohort study • Funding/CoI: not reported • Setting: nationwide registry, Japan • Sample size: N=13566 • Duration: 1995-2001	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ N0M0 ○ Patients without pathologic data, incomplete survival data and without data on operative curability, distant metastasis, or hepatic lymph node metastasis were excluded • *A priori* patient characteristics: ○ Male: 79.5% ○ 60+: 67% ○ HBV: 19.8%; HCV: 66.5% ○ Child-Pugh A: 62.4%	• Number of HCC lesions (including intrahepatic metastasis) • Tumour diameter (largest dimension of tumour specimen) • Portal invasion (none, 3rd branch, 2nd branch, 1st branch or trunk) • Hepatic venous invasion (none, branch of HV, trunk of HV or IVC) • Bile duct invasion (none, intrahepatic bile duct, extrahepatic bile duct) • Grade of differentiation (well, moderately, poorly, undifferentiated) • Background liver (normal, hepatitis, cirrhosis) • Gross classification (type 1, 2 or 3, multinodular type, massive type of Eggel, diffuse type of Eggel) • Hepatic involvement (1 segment, 1 sector, 2 sectors, at least 3 sectors) • Fibrous capsule • Macroscopic intrahepatic metastasis (none, within 1 sector, within 2 sectors, 3 sectors or more)	Significant pathologic factors for OS (RR [95%CI]): • Vascular or bile duct invasion: RR 1.36 (1.29-1.43) • Liver cirrhosis: RR 1.26 (1.20-1.32) • Tumour diameter > 2cm: RR 1.21 (1.14-1.28) • Multiple HCC lesions: RR 1.18 (1.12-1.23) • Hepatic involvement > 1 segment: RR 1.14 (1.09-1.19) • Differentiation: RR 1.14 (1.08-1.20) • Gross classification: RR 1.13 (1.08-1.18)	• Based on the results of the MVA, 3 factors were selected for the LCSGJ-T staging system: vascular or bile duct invasion, diameter, and single/multiple. Patients with 0 factors were T1, with 1 factor T2, 2 factors T3 and 3 factors T4 • 5-year overall survival, LCSGJ-T vs. AJCC-T: ○ T1: 70% vs. 61% ○ T2: 58% vs. 46% ○ T3: 41% vs. 30% ○ T4: 24% vs. -	Level of evidence: C • Population-based study • 5382 patients excluded based on exclusion criteria • Median follow-up: not reported
Ikai 2004	• Retrospective single	• Eligibility criteria:	• Number of HCC lesions	Significant pathologic		Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	cohort study • Funding/CoI: not reported • Setting: nationwide registry, Japan • Sample size: N=12118 • Duration: 1/1990-12/1999	○ Patients with HCC undergoing hepatic resection • *A priori* patient characteristics: ○ Male: 78.9% ○ Mean age: 62.5 years	• Tumour diameter (maximal tumour dimension) • Intrahepatic extent of tumour (H1: 1 segment; H2: 2 segments; H3: 3 segments; H4: >3 segments) • Extrahepatic metastasis • Growth type (expansive or invasive growth) • Septum formation • Portal invasion • Hepatic venous invasion • Bile duct invasion • Surgical curability • Surgical free margin • Background liver • Fibrous capsule	factors for OS (HR [95%CI]): • Tumour diameter > 10cm vs. ≤ 2cm: HR 2.53 (2.07-3.09) • Multiple HCC lesions: HR 1.19 (1.05-1.35) • Intrahepatic extent of tumour (H3/H4 vs. H1 or less): HR 1.03 (??) (1.07-1.57) • Extrahepatic metastasis: HR 2.19 (1.55-3.09) • Portal vein invasion: HR 1.46 (1.31-1.62) • Hepatic vein invasion: HR 1.17 (1.01-1.36) • Surgical curability: HR 1.40 (1.18-1.65) • Surgical free margin: HR 1.10 (1.01-1.20)		• Population-based study • Dropouts not discussed • Median follow-up: 21.5 months (range 0.03-119.7 months)
Zhang 2000	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, China • Sample size: N=1457 • Duration: 1/1990-12/1995	• Eligibility criteria: ○ Patients with HCC undergoing curative or relatively curative hepatic resection • *A priori* patient characteristics: ○ Male: 87.5% ○ Mean age: 49.0 years ○ Preoperative TACE: 8.2%	• Intraoperative lesion number • Extent of resection • Surgical margin • Intraoperative tumor thrombus • Tumour size • Tumour gross type • Pathologic type • Edmondson16 classification • Tumour growth style • Capsular invasion • Daughter nodules • Vascular invasion • Cirrhosis • pTNM stage	Significant pathologic factors for DFS: • Daughter nodules: HR 9.259, p<0.001 • Vascular invasion: HR 2.662, p=0.007 • Intraoperative thrombus: HR 0.247, p=0.005 • Tumour size: HR 1.374, p=0.010 • Tumour gross type: HR 0.202, p=0.003		Level of evidence: C • Follow-up results not obtained for 268/1725 cases: excluded from analysis • Median follow-up: not reported • No clear definitions of prognostic factors provided
Qiang 2006	• Retrospective single cohort study • Funding/CoI: supported by the Department of Hepatobiliary Surgery, Cancer Hospital of	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection • *A priori* patient characteristics:	• Number of nodules • Tumour capsule • Tumour size of main nodule • Vascular invasion (portal or hepatic vein	Significant pathologic factors for DFS (RR [95%CI]): • Vascular invasion: RR 2.72 (2.31-3.20) • Liver cirrhosis: RR 1.46		Level of evidence: C • Lost-to-follow-up: 3.46% • Median follow-up: not reported

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	Tianjin Medical University, and Division of Community Health, Memorial University of Newfoundland, St. John's, Newfoundland, Canada; CoI not reported • Setting: single university centre, China • Sample size: N=1157 • Duration: 1/1998-12/2003	○ Male: 87.6% ○ Age: 16-85 years ○ HBV: 89% ○ Child-Pugh A: 29.1%	invasion) • Cirrhosis	(1.13-1.87) • Tumour diameter > 5cm: RR 2.21 (1.85-2.63) • Multiple nodules: RR 2.69 (2.22-3.24) • Tumour capsule: RR 1.67 (1.40-1.99)		
Fan 2009	• Retrospective single cohort study • Funding/CoI: supported by combined grants from National Natural Science Foundation of China (No.30873039, 30571801), Shanghai Science and Technology Development Funds (No.06QA14012, No.054119530), Foundation of Shanghai Science Technology Commission (No. 07JC14010, 06xD14004, 044119608 and 07SP07003), the National Key Sci-Tech Special Project of China (No.2008ZX10002-022), and the Program for Excellent Disciplinary Leaders of Shanghai Health Bureau (No.LJ06004) • Setting: 7 centres, China • Sample size: N=1078 • Duration: 4/2001-5/2007	• Eligibility criteria: ○ Patients with HCC undergoing liver transplantation • *A priori* patient characteristics: ○ Male: 90.0% ○ Median age: 49.0 years ○ HBV: 85.3%; HCV: 3.2% ○ Cirrhosis: 90.4% ○ Child-Pugh A: 47.0%	• Cirrhosis • Tumour differentiation (modified Edmondson) • Total tumour size (sum of maximal diameter of each lesion) • Number of nodules • Tumour satellite • Tumour site (left lobe, right lobe, bilobe) • Tumour capsule • Lymph node invasion • Macrovascular invasion • Microvascular invasion • pTNM (UICC)	Significant pathologic factors for OS (HR [95%CI]): • Tumour differentiation: HR 1.46 (1.16-1.84) • Total tumour size (≤9 vs. >9 cm): HR 1.74 (1.31–2.32) • Tumour number > 3: HR 1.50 (1.09–2.08) • Macrovascular invasion: HR 1.38 (1.05-1.83)	Significant pathologic factors for DFS (HR [95%CI]): • Tumour differentiation: HR 1.62 (1.33–1.98) • Total tumour size (≤9 vs. >9 cm): HR 1.71 (1.33–2.18) • Tumour number > 3: HR 1.41 (1.07–1.86) • Tumour capsule: HR 0.74 (0.56–0.98) • Macrovascular invasion: HR 1.56 (1.23-1.96)	Level of evidence: C • Lost-to-follow-up: N=81 • Mean follow-up: 35.3 months • Consecutive patient inclusion
Wu 2011	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC	• Cirrhosis • Tumour grade	**HCC size > 5 cm**	**HCC size < 5 cm**	Level of evidence: C

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	• Funding/CoI: no CoI to declare • Setting: single university centre, Taiwan • Sample size: N=1048 • Duration: 1/1999-6/2005	undergoing liver resection • *A priori* patient characteristics: ○ Male: 79.8% ○ Mean age: 56.3 years ○ HBV: 62.3%; HCV: 29.9%	(Edmondson) • Tumour size • Resection weight • Tumour satellite • Tumour rupture • Tumour capsule • Vascular invasion • Steatosis	Significant pathologic factors for OS (OR [95%CI]): • Vascular invasion: OR 2.30 (1.69-3.12) • Steatosis: OR 0.67 (0.47-0.95) Significant pathologic factors for DFS (OR [95%CI]): • Vascular invasion: OR 1.79 (1.37-2.33) • Cirrhosis: OR 1.36 (1.05-1.77)	Significant pathologic factors for OS (OR [95%CI]): • Vascular invasion: OR 1.64 (1.21-2.21) • Cirrhosis: OR 1.70 (1.21-2.38) Significant pathologic factors for DFS (OR [95%CI]): • Vascular invasion: OR 1.29 (1.01-1.64) • Cirrhosis: OR 1.79 (1.39-2.29)	• Dropouts: not reported • Median follow-up: 53.1 months • No clear definition of most pathologic factors
Nathan 2009	• Retrospective single cohort study • Funding/CoI: Support by grant 1KL2RR025006-01 from the National Center for Research Resources (NCRR) • Setting: SEER database, US • Sample size: N=788 • Duration: 1988-2005	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection (not ablation or transplantation) ○ Patients with tumors >5 cm in size or missing size data, extrahepatic tumor extension, or major vascular invasion were excluded ○ Patients with nodal disease (N1) or unknown N classification and patients with metastatic disease (M1) or unknown M classification were excluded • *A priori* patient characteristics: ○ Male: 70% ○ Median age: 63 years	• Tumour grade (well, moderately, poorly, undifferentiated, unknown) • Tumour size • Microvascular invasion • Number of nodules • Cirrhosis	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 1.44 (1.11-1.86) • Tumour size >2 cm: HR 1.51 (1.12–2.03) • Multifocality: HR 1.44 (1.11–1.86) • Cirrhosis: HR 1.67, p=0.003 (subset of 253 patients)		Level of evidence: C • Consecutive patients • Dropouts not reported • Median follow-up not reported
Shimada 2005	• Retrospective single cohort study • Funding/CoI: Supported by a Grant-in-Aid for cancer research from the Ministry of Health,	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ Surviving at least 1 month after surgery	• Tumour size • Resection margin • Number of nodules • Portal vein invasion • Intrahepatic metastases • Background liver	Significant pathologic factors for 10-year OS (OR [95%CI]): • Intrahepatic metastases: OR 2.48 (1.31-4.68)		Level of evidence: C • Dropouts: 8 patients who were lost to follow-up, and 14 patients who died of

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	Labor, and Welfare of Japan • Setting: single centre, Japan • Sample size: N=481 • Duration: 1/1987-12/1993	and discharge from hospital after surgery • *A priori* patient characteristics: ○ Male: 79.6% ○ Mean age: 60 years ○ Preoperative TACE: 68.4%	parenchyma	• Portal vein invasion: OR 1.98 (1.05-3.74) • Noncancerous liver parenchyma: OR 3.09 (1.69-5.64) • Solitary nodule: OR 3.12 (1.62-6.02)		non-cancer causes within 10 years of the surgery were excluded from the study • Median follow-up: 6 years
Vauthey 2002	• Retrospective single cohort study • Funding/CoI: not reported • Setting: 4 centres, multinational • Sample size: N=557 • Duration: 1980-1998	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ Surviving at least 1 month after surgery ○ Patients with incomplete survival data were excluded • *A priori* patient characteristics: ○ Male: 69% ○ Mean age: 59 years ○ HBV: 36% ○ Child-Pugh A: 83%	• Fibrosis stage • Tumour size (largest dimension of tumour specimen) • Number of nodules • Tumour location (unilobular, bilobular) • Microvascular invasion • Macrovascular invasion • Edmondson Steiner	Significant pathologic factors for OS (HR [95%CI]): • Major vascular invasion: HR 2.1 (1.4-3.3) • Microvascular invasion: HR 1.6 (1.2-2.1) • Tumour size >5 cm: HR 1.4 (1.1–1.9) • Multifocality: HR 1.5 (1.1–1.9) • Severe fibrosis/cirrhosis: HR 1.6 (1.2-2.2)		Level of evidence: C • Dropouts not reported • Median follow-up: 35 months
Regimbeau 2004	• Retrospective single cohort study • Funding/CoI: not reported • Setting: 4 centres, multinational • Sample size: N=547 • Duration: 1980-1999	• Eligibility criteria: ○ Patients with HCC undergoing curative partial hepatic resection ○ Exclusion of patients who died of unknown causes (N=28) or with follow-up < 1 year (N=16) • *A priori* patient characteristics: not presented for entire cohort	• Fibrosis grade • Hepatitis grade • Tumour size (largest dimension of tumour specimen) • Number of nodules • Tumour location (unilobar, bilobar) • Histopathologic type (microtrabecular, macrotrabecular, acinar, diffuse) • Tumour grade (Edmondson) • Degree of necrosis • Fibrous capsule • Minor vascular invasion • Major vascular invasion • Nuclear polymorphism (mild, moderately, marked) • Resection margin	Significant pathologic factors for early death due to recurrence (OR [SE]): • Nuclear polymorphism: OR 3.0 (0.52) • Tumour size >5 cm: OR 3.0 (0.51) • Multifocality: OR 3.3 (0.50)		Level of evidence: C • Median follow-up: 33 months • Dropouts not reported • Very probably same patients as Vauthey 2002

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Zhou 2010	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, China • Sample size: N=528 • Duration: 1/2000-4/2005	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection • *A priori* patient characteristics: ○ Male: 86.9% ○ Median age: 65.8 years ○ HBV: 36.3%; HCV: 46.4%	• Tumour differentiation (Edmondson) • Vascular invasion • TNM stage • pAkt expression • PTEN expression • p27 expression • pS6 expression	Significant pathologic factors for OS (OR [95%CI]): • Tumour differentiation: OR 2.15 (1.32-1.51) • Vascular invasion: OR 4.98 (1.46-12.01) • TNM stage: OR 2.32 (1.11-3.09) • pAkt expression: 2.96 (1.18-10.79) • PTEN expression: 2.61 (1.69-3.98) • p27 expression: OR 1.69 (1.12-2.55) • pS6 expression: OR 3.86 (1.71-8.76)		Level of evidence: C • Consecutive patient inclusion • Median follow-up: 42 months • Vascular invasion not clearly defined
Yang 2009	• Retrospective single cohort study • Funding/CoI: Supported by National Key Technologies R and D Program of China, (2001BA703B04, 2004BA703B02), National Keystone Basic Research Program of China (2004CB720303), National Science Fund for Distinguished Young Scholars of China (30328028), National Natural Science Foundation of China (30571826), and National High Technology Research and Development Program of China (2006AA02Z4B2); CoI not reported • Setting: single centre, China • Sample size: N=481 • Duration: 1/1992-12/2002	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection • *A priori* patient characteristics: ○ Male: 89.4% ○ Age ≥ 50: 42.8% ○ HBV: 92.5% ○ Child-Pugh A: 81.1%	• Cirrhosis • Tumour size • Degree of necrosis • Fibrous capsule • Vein invasion • Edmondson-Steiner Grade • Tumour nodule number	Significant pathologic factors for OS (HR [95%CI]): • Vein invasion: HR 48.74 (4.76-498.37)		Level of evidence: C • Consecutive patient inclusion • Median follow-up: 38 months • Dropouts not reported • No clear definition of prognostic factors

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Wang 2009	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single university centre, Taiwan • Sample size: N=473 • Duration: 1/1993-12/2002	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection with curative intent • *A priori* patient characteristics: ○ Male: 80.1% ○ Mean age: 53.1 years ○ HBV: 68.5%; HCV: 28.9% ○ Child-Pugh A: 83.3%	• Histopathology of non-tumour tissue • Adjacent tissue invasion • Tumour size (largest diameter of tumour) • Number of nodules (single vs. multiple) • Tumour location (unilateral, bilateral) • Microvascular invasion • Daughter nodule • Resection margin	Significant pathologic factors for DFS (RR [95%CI]): • Microvascular invasion: RR 1.85 (1.41-2.42) • Liver cirrhosis: RR 1.83 (1.40-2.40) • Tumour diameter > 10cm: RR 2.07 (1.34-2.90) • Bilateral disease: RR 2.22 (1.16-4.26) • Daughter nodule: RR 2.18 (1.58-3.01)		Level of evidence: C • Consecutive patient inclusion • Mean follow-up: 3.6 years • Dropouts not reported
Duffy 2007	• Retrospective single cohort study • Funding/CoI: grant support from The George T. Pfleger Foundation, The DuMont Foundation, The JoAnn Barr Foundation, Dr. Soliman Fakeeh, The W.K. Day Foundation, and Mr. Gilbert I. Garfield; CoI not reported • Setting: single centre, US • Sample size: N=467 • Duration: 1984-2006	• Eligibility criteria: ○ Patients with HCC undergoing orthotopic liver transplantation • *A priori* patient characteristics: ○ Male: 60% ○ Mean age: 57 years ○ HBV: 17%; HCV: 55%	• Multifocal tumour • Lymphovascular invasion • Tumour differentiation (well, moderately, poorly) • Tumour size	Significant pathologic factors for OS: • Multifocal tumour: HR 0.22, p<0.001 • Lymphovascular invasion: HR 2.44, p<0.001 • Tumour differentiation: HR 4.53, p=0.002		Level of evidence: C • Mean follow-up: 6.6 years • Dropouts not reported
Lim 2011	• Retrospective single cohort study • Funding/CoI: Supported by the Khoo Clinical Discovery Project Award of the Duke-NUS Graduate Medical School; CoI not reported • Setting: two centres, Singapore • Sample size: N=454 • Duration: 1/2000-3/2009	• Eligibility criteria: ○ Patients with HCC undergoing curative hepatic resection ○ No concomitant non-HCC cancers • *A priori* patient characteristics: ○ Male: 81% ○ Mean age: 61.3 years ○ HBV: 66% ○ Child-Pugh A: 93%	• Cirrhosis • Adjacent tissue invasion • Tumour size (size of largest tumour) • Number of nodules • Tumour grade (Edmondson) • Microvascular invasion • Resection margin	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 2.12 (1.52-2.97) • Invasion of contiguous organs: HR 2.74 (1.08-6.94) • Cirrhosis: HR 1.49 (1.07-2.07)		Level of evidence: C • Median follow-up: 27.7 months • Dropouts not reported
Pawlik 2004	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC undergoing hepatic	• Cirrhosis • Tumour size (largest	Significant pathologic factors for OS (HR [95%CI]):		Level of evidence: C • Median follow-up: 33

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
	• Funding/CoI: not reported • Setting: 5 centres, multinational • Sample size: N=446 • Duration: 1990-2000	resection ○ Complete HBV and HCV serology • *A priori* patient characteristics: not reported for entire group ○ HBV: 54%; HCV: 35%	diameter of tumour specimen) • Number of nodules • Tumour location • Microvascular invasion • Macrovascular invasion	• Microvascular invasion: HR 1.88 (1.44-2.46) • Macrovascular invasion: HR 2.36 (1.50-3.72) • Firbosis/cirrhosis: HR 2.16 (1.48-3.15)		months • Dropouts not reported • Potential overlap with Vauthey 2002 and Regimbeau 2004
Lei 2006	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: single centre. Taiwan • Sample size: N=440 • Duration: 7/1991-1/1999	• Eligibility criteria: ○ Patients with HCC undergoing hepatic resection ○ Patients dying in the hospital before discharge were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 86.8% ○ Mean age: 59.6 years ○ HBV: 65.7%; HCV: 22%	• Fibrosis score • Adjacent tissue invasion • Tumour size • Number of nodules • Tumour location (unilobar, bilobar) • Microvascular invasion • Resection margin • Macrovascular invasion • Major vascular invasion • Tumour rupture • Edmondson-Steiner grading • Tumour DNA ploidy	Significant pathologic factors for OS (HR [95%CI]): • Microvascular invasion: HR 1.48 (1.12-1.95) • Major vascular invasion: HR 2.3676 (1.88-3.78) • Surgical margin < 1cm: HR 1.65 (1.29-2.12) • Multiple tumours: HR 1.59 (1.23-2.05) • Tumour rupture: HR 1.76 (1.22-2.53)		Level of evidence: C • Median follow-up: 66 months • Dropouts not reported
Wang 2010	• Retrospective single cohort study • Funding/CoI: supported by the Special Research Foundation of the National Nature Science Foundation of China (30872487); no CoI to declare • Setting: single university centre, China • Sample size: N=438 • Duration: 1/1991-12/2004	• Eligibility criteria: ○ Patients with HCC undergoing partial hepatic resection ○ Patients dying in the hospital before discharge were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 86.8% ○ Mean age: 50 years	• Tumour size (sum of largest dimension of each nodule) • Number of nodules • Tumour location (unilobar, bilobar) • Capsular invasion • Satellite nodules • Resection margin • Macrovascular invasion • Lymph node metastasis • Extrahepatic metastasis • Histological grade (G1, G2, G3) • Tumour stage (AJCC)	Significant pathologic factors for OS (95%CI, p value): • Tumour size: 1.17-1.6, p<0.001 • Capsular invasion: 0.48-0.99, p=0.047 • Resection margin: 0.5-0.91, p=0.011 • Macrovascular invasion: 1.18-1.56, p=0.003 • Tumour stage: 1.14-1.43, p<0.001		Level of evidence: C • Median follow-up: 21 months • 46 (10.5%) patients lost to follow-up
Lauwers 2002	• Retrospective single cohort study • Funding/CoI: not reported • Setting: multicentre, multinational • Sample size: N=425 • Duration: 1980-1998	• Eligibility criteria: ○ Patients with HCC undergoing complete resection and with complete histopathologic information ○ Patients who died within 30 days after	• Microvascular invasion • Nuclear grade (mild, moderate, severe atypia) • Mitosis activity • Tumour architecture (microtrabecular, macrotrabecular,	Significant pathologic factors for OS: • Microvascular invasion: p<0.001 • Nuclear grade 3: p=0.008		Level of evidence: C • Median follow-up: 62 months for survivors, 27 months for patients who died • Dropouts not reported • Same patients as

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		resection or lost to follow-up were excluded from the analysis ○ Pure fibrolamellar HCCs and hepatocholangio-carcinomas were not included • *A priori* patient characteristics: not reported for entire group ○ Male: 70% ○ Median age: 62 years	compact, acinar) • Tumour necrosis • Growth interface (sinusoidal, replacing, pseudocapsular, capsular)			Vauthey 2002
Wu 2005	• Retrospective single cohort study • Funding/CoI: not reported • Setting: single centre, Taiwan • Sample size: N=426 • Duration: 1991-2002	• Eligibility criteria: ○ Patients with cirrhosis and HCC undergoing elective curative hepatectomy ○ Patients with recurrent HCC whose first liver resection was carried out elsewhere and those who underwent emergency surgery for ruptured HCC were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 77.6% in period 1, 81.1% in period 2 ○ Median age: 56.5 and 61.1 years	• Tumour size • Number of nodules • Tumour capsule • Satellite nodules • Resection margin • Vascular invasion • Tumour grade (Edmondson) • Tumour stage (UICC)	Significant pathologic factors for OS (RR [95%CI]): • TNM stage II: RR 0.26 (0.15-0.46) • TNM stage III: RR 0.48 (0.29-0.63)	Significant pathologic factors for DFS (RR [95%CI]): • TNM stage II: RR 0.73 (0.57-0.93) • TNM stage III: RR 0.88 (0.73-1.07)	Level of evidence: C • Median follow-up: 49.6 and 40.1 months • Dropouts not reported • No clear definition of vascular invasion
Zhang 2009	• Retrospective single cohort study • Funding/CoI: no CoI to report • Setting: single university centre, China • Sample size: N=412 • Duration: 10/1996-10-2006	• Eligibility criteria: ○ Patients with liver cirrhosis and newly diagnosed HCC undergoing liver resection • *A priori* patient characteristics: not reported for entire group ○ Male: 79.6% ○ Median age: 52 years ○ Child-Pugh A: 82%	• Tumour size • Number of nodules • Tumour location (unilobar, bilobar) • Tumour capsule • Resection margin • Vascular invasion (portal or hepatic vein invasion) • TNM stage (UICC)	Significant pathologic factors for OS: • Tumour location (1 lobe/2 lobes): HR 4.93 • Vascular invasion: HR 2.82 • Tumour capsule: HR 2.51	Significant pathologic factors for DFS: • Tumour location (1 lobe/2 lobes): HR 48.81 • Vascular invasion: HR 3.97 • Tumour capsule: HR 2.39	Level of evidence: C • Median follow-up: 21 months • 10% (46/458) were lost in follow-up

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Vauthey 2007	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: multicentre, multinational • Sample size: N=489 • Duration: 1985-2005	• Eligibility criteria: ○ Patients who underwent liver transplantation for HCC ○ Patients with fibrolamellar variant of HCC and those who died postoperatively were excluded • *A priori* patient characteristics: not reported for entire group ○ Male: 81.8% ○ Median age: 56 years ○ Child-Pugh A: 23.5% ○ HCV: 48.6%; HBV: 18.1%	The following staging systems were evaluated: • AJCC/UICC • Japanese TNM • Pittsburgh • UNOS • CLIP • Japan Integrated Staging • Barcelona Clinic Liver Cancer	• In only three systems - AJCC/UICC, Japanese TNM and Pittsburgh - were OS and RFS longer for patients with low stage vs. more advanced stage	For OS and RFS, sequential stages were different only for AJCC/UICC: • OS: ○ II vs. I: HR 1.58 (1.08-2.30) ○ IIIA vs. II: HR 1.995 (1.25-3.19) • RFS: ○ II vs. I: HR 1.74 (1.21-2.49) ○ IIIA vs. II: HR 2.01 (1.29-3.14)	Level of evidence: C • Consecutive patient inclusion • Median follow-up: 40 months • Dropouts not reported
Eguchi 2011	• Retrospective single cohort study • Funding/CoI: no CoI to declare • Setting: nationwide, Japan • Sample size: N=1199 • Duration: 1988-2003	• Eligibility criteria: ○ Patients with HCC who had undergone liver resection with curative intent ○ Patients who survived more than 10 years without recurrence of HCC (N=281) and those who died from recurrent HCC within 5 years of liver resection were identified (N=918) • *A priori* patient characteristics: 10y RFS vs. died within 5 years ○ Male: 77.9% vs. 82.2% ○ Median age: 57.5 vs. 60.8 years ○ Child-Pugh A: 79.1% vs. 65.1% ○ HCV: 52.0% vs. 75.1%; HBV: 32.2% vs. 22.0%	• Tumour size • Number of nodules • Intrahepatic metastases • Non-cancerous liver (normal, chronic hepatitis, fibrosis, cirrhosis) • Vascular invasion (microscopic portal vein invasion?) • Tumour differentiation (well, moderate, poor, unknown) • Macroscopic type: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) or unknown	Significant pathologic factors for death from recurrence within 5 years (OR [95%CI]): • Tumour size >5 cm: OR 2.56 (1.16-5.65) • Poor tumour differentiation: OR 3.33 (1.46-7.60) • Intrahepatic metastasis: OR 2.34 (1.02-5.37)		Level of evidence: C • Median follow-up: 11.2 and 0.9 years respectively • Dropouts not reported
Liu 2009	• Retrospective single cohort study	• Eligibility criteria: ○ Patients with HCC	• Tumour size • Liver cirrhosis	Significant pathologic factors for RFS (HR		Level of evidence: C

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	• Funding/CoI: supported by the Research Foundation from Shanghai Municipal Education Commission, PR China, No 06CZ016; no CoI to declare • Setting: single university centre, China • Sample size: N=458 • Duration: 1/2002-6/2005	who had undergone liver resection • *A priori* patient characteristics: ○ Male: 71.4% ○ Median age: not reported ○ HBV: 76.2%	• Intrahepatic metastases • Tumour capsule • Histological grade (well, moderately, poor) • P53 • Ki67 • BUBR1 overexpression	[95%CI]): • Intrahepatic metastasis: HR 2.32 (1.24-4.72) • P53: HR 2.67 (1.25-6.84) • BUBR1: HR 3.25 (1.42-7.9)		• Median follow-up: not reported • Lost to follow-up: 19.5%